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Review article

"Current concepts of mechanical ventilation in neonates" – Part 1: Basics

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ABSTRACT

Mechanical ventilation is potentially live saving in neonatal patients with respiratory failure. The main purpose of mechanical ventilation is to ensure adequate gas exchange, including delivery of adequate oxygenation and enough ventilation for excretion of CO_2. The possibility to measure and deliver small flows and tidal volumes have allowed to develop very sophisticated modes of assisted mechanical ventilation for the most immature neonates, such as volume targeted ventilation, which is used more and more by many clinicians. Use of mechanical ventilation requires a basic understanding of respiratory physiology and pathophysiology of the disease leading to respiratory failure. Understanding pulmonary mechanics, elastic and resistive forces (compliance and resistance), and its influence on the inspiratory and expiratory time constant, and the mechanisms of gas exchange are necessary to choose the best mode of ventilation and adequate ventilator settings to minimize lung injury. Considering the pathophysiology of the disease allows a physiology-based approach and application of these concepts in daily practice for decision making regarding the use of modes and settings of mechanical ventilation, with the ultimate aim of providing adequate gas exchange and minimising lung injury.

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1. Introduction

Mechanical ventilation is an extraordinary life-saving intervention for sick neonates with respiratory failure. However, ventilator-induced lung injury (VILI) caused by mechanical ventilation contributes to significant morbidity and mortality in neonates. The pathophysiology of lung damage due to mechanical ventilation is multi-factorial. The goal of mechanical ventilation is to oxygenate the baby and to remove carbon dioxide, and while doing so, attempt to minimize damage to the lungs. Historically, positive pressure ventilation is the most commonly used method of ventilation in neonates [1].

Volume-targeted ventilation became the ventilation mode of choice in neonates over the last decade by measuring a small volume of delivered gases using advanced technology. Furthermore, advances in ventilator technology were leading to the development of several modes of ventilation that attempt to make mechanical ventilation gentler and more physiological for a spontaneously breathing neonate in an attempt to reduce lung injury. In the first part of two review articles, we will discuss the basic mechanics of neonatal ventilation physiology covering underlying mechanisms of gas transport in neonatal invasive mechanical ventilation, physiologic dead space, oxygenation, ventilation and perfusion, viscous and airway resistance, surface tension, work of breathing, time constant, and compliance (static and dynamic) of respiratory system.

2. Basic mechanics of neonatal mechanical ventilation

Millions of alveoli make up the distal respiratory system. The

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alveolar surface is partitioned to provide a large surface area to facilitate gas exchange.

2.1. Inspiration

Spontaneous inspiration is an active process. The lung is expanded during inspiration by forces generated primarily by the diaphragm but also by the intercostal muscles. This force causes the intrapleural pressure to decrease, and gas flows from the atmosphere into the lungs. In newborns, the thorax is more cylindrical as compared to older children or adults, where it has a more ellipsoid shape. The neonatal ribs are more horizontal compared to oblique in older children or adults. Because of this, newborns have less mechanical advantage of elevating the ribs to increase intrathoracic volume during inspiration. In newborns, the insertion of the diaphragm is more horizontal, and intercostal muscles provide only little support during inspiration. Because of these reasons, respiratory distress in a newborn increases the risk of respiratory muscle fatigue and, consequently, respiratory failure.

Clinical relevance: The inspiratory time (i-time) is approximately 0.30–0.35 s in spontaneously breathing preterm and 0.35–0.40 s in full-term infants. Studies have shown that very preterm babies breathe faster and may have an i-time as short as 0.2–0.27 s [2]. However, this may not be sufficient for adequate oxygenation and ventilation if the lungs are stiff. Often, the term newborn requires i-time of 0.3–0.4 s. Increasing i-time is one of the possible maneuvers to improve oxygenation. Inspiration on a ventilator is driven by the flow of air into the lungs generating pressure to open up the lungs and drive gas (air or oxygen) into the lungs.

2.2. Expiration

Expiration is usually a passive process. Elastic recoil is the main driving force during expiration. It depends upon three components; a) surface tension produced by an air-liquid interface, b) lung tissue elastic elements, and c) the structure/development of the rib cage [3]. In preterm babies with RDS, the most significant contributor to elastic recoil is surface tension due to surfactant deficiency in alveoli and terminal airways. The collapse at the end of expiration can lead to atelectasis. Positive end-expiratory pressure may be applied to the infant's airway to counteract the tendency toward collapse and the development of atelectasis and also to establish functional residual capacity (FRC).

Clinical relevance: Establishment of FRC and prevention of alveolar collapse by using effective PEEP at the end of expiration or CPAP is essential. Expiration is a passive process, but an obstruction to flow out of the lung may cause gas trapping. This is seen with increased secretions, inflammation, and with tracheo/bronchomalacia as in chronic lung disease.

2.3. Compliance

Compliance (C) is the ease with which the lung can be distended. It can be described a measure of the change in volume (V) resulting from a given change in pressure (P) and measured using the formula ($C = V/P$).

Clinical relevance: A lung which is surfactant deficient as in Respiratory Distress Syndrome (RDS) is stiff and cannot be distended easily and hence has low compliance. A lung which has hyperinflated areas as in Bronchopulmonary Dysplasia (BPD) can be easily be distended and hence is described to have high compliance.

2.3.1. Static compliance

Compliance measured under static conditions reflects only the elastic properties of the lung. Static compliance is measured by determining the transpulmonary pressure change after inflating the lungs with a known volume of gas. [4] The static pressure-volume curve illustrates the relationships between different forces at various levels of lung expansion (Fig. 1). In newborns, the chest wall is very compliant; thus, substantial volume changes can be achieved with small pressure changes if lung compliance is normal. Both lung and chest wall compliance together give the total respiratory system compliance.

2.3.2. Dynamic compliance

Measurement of compliance during continuous breathing is called dynamic compliance. This is generally measured in clinical settings, but the interpretation is more difficult. It reflects the elastic properties of the lung but is also influenced by resistive components. It is dependent on the magnitude of airflow and thus on the newborn's breathing rate. Therefore, in neonates with a high respiratory rate, dynamic compliance may underestimate static compliance. The dynamic pressure-volume loop illustrates the pressure-volume relationship during inspiration and expiration (Fig. 2) in a healthy lung, and it would be more flat in a lung with respiratory distress syndrome (decreased compliance) [5].

Lung compliance divided by functional residual capacity (FRC) is called specific lung compliance. The dynamic pressure-volume loops illustrate the pressure-volume relationship at different lung volumes (Fig. 3). The overall compliance curve is sigmoidal. At the lower end of the curve (at low lung volume), the compliance is low. That is, there is only a small change in volume for a given change in pressure (Fig. 3A). This correlates with underinflation (atelectasis). At the center of the curve, more lung volume is recruited, the curve is steeper, and thus, the compliance is higher; there is a more significant change in volume for a given change in pressure (Fig. 3B). Ideally, normal tidal breathing should occur at this position of the lung expansion curve. At the upper end of the curve (at high lung volume), the compliance is low; again, there is a small change in volume for a given change in pressure (Fig. 3C). This correlates with a lung, or at least parts of the lung, being already overinflated. It is essential to understand that compliance is reduced at both high and low lung volumes. Unfortunately, lung mechanics are not homogenous in lungs with disease, and thus, the relationship mentioned above is somewhat simplified.

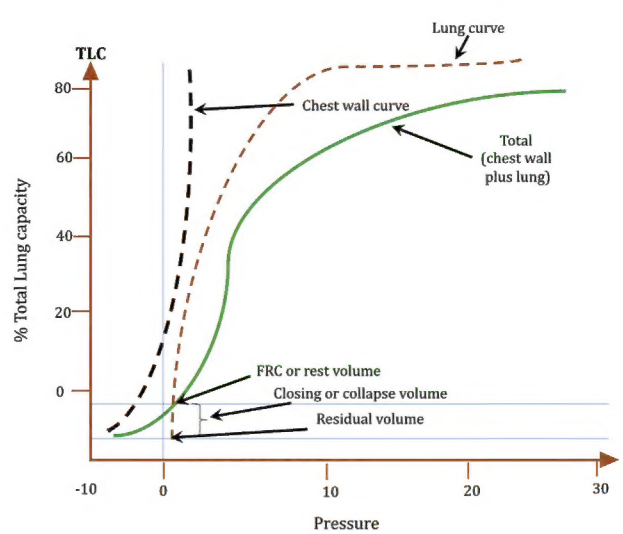

Fig. 1. The static pressure-volume curve (Adopted from Goldsmith et al.).

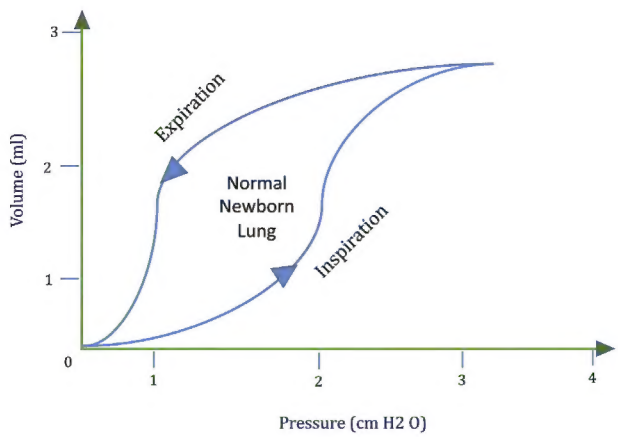

Fig. 2. Dynamic pressure-volume curve (Adopted from Goldsmith et al.).

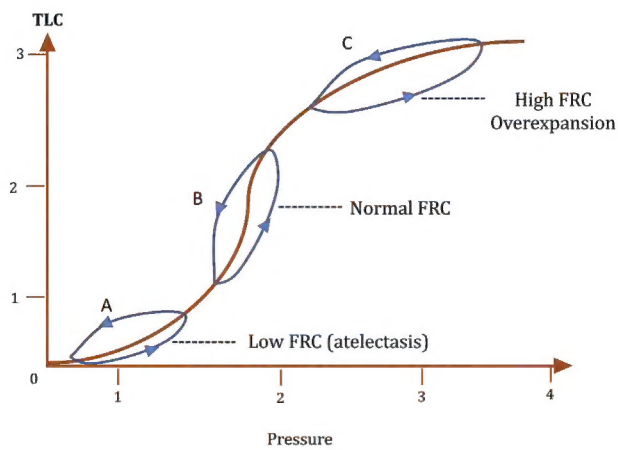

Fig. 3. Extended compliance or lung expansion curve (Adopted from Goldsmith et al.).

Clinical relevance: Low lung volumes are seen in surfactant deficiency states (Respiratory Distress Syndrome (RDS)), whereas high lung volumes are seen in obstructive lung diseases, such as Bronchopulmonary Dysplasia (BPD).

2.4. Resistance

Two types of resistance are present in the respiratory system [6]. The resistance within the lung tissue during inflation and deflation is called viscous resistance. In neonates, viscous resistance is elevated because immature small lungs contain relatively fewer terminal air spaces, high tissue density, and more interstitial fluid, especially during the early transition after birth.

Airway resistance is the resistance that occurs between moving molecules in the gas stream and along the wall of the respiratory system. Airway resistance is relatively high in newborns because of the small diameter of the airways in the newborn lung. It is determined by flow velocity, length of conducting airways, viscosity and density of gases, and inside diameter of the airways. Resistance to flow depends upon whether the flow is laminar or turbulent. Reynolds number ($Re = 2\ r\ v\ d/n$) is used as an index to determine this flow. Where r is the radius, v is the velocity, d is the density, and n is the viscosity. If the Reynolds number is higher than 2000, then turbulent flow is very likely (if the tube has a large radius, a high velocity, a high density, or a low viscosity). If flow is laminar resistance to flow of gas through a tube is described by Poiseuille's law (Resistance (R) and is directly proportional to (L) length of the tube and (n) viscosity of the gas. It is inversely proportional to the fourth power of radius (r) [4]). Thus, additional resistance is noted during invasive mechanical ventilation as the gas passes through the ventilator circuit and the endotracheal tube. Resistance is linearly proportional to tube length. The shorter the endotracheal tube, the lower the resistance. Resistance is inversely proportional to the radius of the endotracheal tube. Therefore, a reduction in the radius by half results in a 16-fold increase in resistance, indicating that the airway diameter is a crucial factor for resistance. Resistance is usually lower during inspiration, as lung distending forces (negative intrathoracic pressure during spontaneous breathing or positive airway pressure during mechanical ventilation) increase the diameter of the tracheobronchial system during inspiration.

In simplistic terms, resistance is viscous resistance plus airway resistance, and it is measured as the pressure needed to flow 1 L of gas through a tube in 1 s. It is defined ($R = (P1 - P2)/V$) as the pressure gradient ($P1 - P2$) required to move gas through the airways at a constant flow rate (V or volume per unit of time).

Clinical relevance: Therefore, high viscous resistance lungs need a higher inspiratory transpulmonary pressure; and high airway resistance lungs need longer in- and expiratory time to in- and deflate.

2.5. Surface tension

Elastic recoil refers to the tendency of stretched elements (chest wall, diaphragm, and lungs) to return to their original shape. The main contributor to lung elastic recoil in the newborn is surface tension. The Laplace relationship ($P = 2\ ST/r$) describes the pressure required to counteract the tendency of the bronchioles and terminal air spaces to collapse. Pressure (P) needed to stabilize the system is directly proportional to twice the surface tension (2 ST) and inversely proportional to the radius of curvature (r). The surface tension forces at the air-liquid interfaces in the distal bronchioles and terminal airways decrease the surface area of the air-liquid interfaces. Surfactant is a surface-active material released by type II pneumocytes. It decreases surface tension and thereby prevents further lung deflation below resting volume at end-expiration and allows an increase in surface tension upon lung expansion that facilitates elastic recoil at the end of inspiration.

Clinical relevance: In preterm babies with RDS, it takes a few days for the endogenous surfactant to be produced, and hence surfactant may be instilled into the lungs after birth if significant RDS with significantly impaired pulmonary mechanics and gas exchange develops.

2.6. Work of breathing

The work of breathing is proportional to the force generated to overcome the frictional resistance and static elastic forces that oppose lung expansion and gas flow into and out of the lungs. It is the integrated product of the pressure (force) and volume (displacement).

It is well represented in the area under the pressure-volume curve in Fig. 4. Hence, workload depends on the elastic properties of the lung and chest wall, airway resistance, tidal volume, and respiratory rate. The areas ABCA and ACDA in Fig. 4 represent the inspiratory work and the expiratory work, respectively, performed to overcome frictional resistance. The area ABCEA represents the total work of breathing during a single breath.

Clinical relevance: Therefore, in practical terms, a stiff RDS lung with low compliance and low resistance will empty very quickly on expiration and has a short time constant and therefore, can be

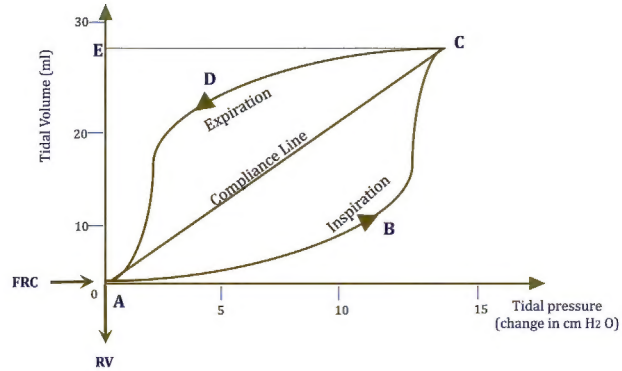

Fig. 4. Pressure-volume loop showing work of breathing and the compliance line (Adopted from Goldsmith et al.).

ventilated using high ventilator rates or even by using high-frequency ventilation. However, in BPD lungs, which have high compliance and high resistance, the lung needs a longer time to fill and empty and has a long time constant, and therefore slow ventilator rates are more useful for ventilatory support.

2.7. Time constant

The time constant of a patient's respiratory system is a measure of how quickly the lungs can inflate or deflate. It means how long it takes for alveolar and proximal airway pressure to equilibrate. The time constant may be influenced by both, changes in elastic and resistive forces. The expiratory time constant (K_t) of the respiratory system is directly related to both lung compliance (C_L), which is the inverse of elastic recoil, and airway resistance (R_{aw}). One time constant of the respiratory system is defined as the time it takes the alveoli to empty 63% of its tidal volume through the airways to the mouth or ventilator. By the end of three-time constants, 95% of the tidal volume is emptied from the lungs. Inspiratory time constants are shorter than expiratory time constants, largely because airway diameter increases during inspiration. Working knowledge of time constants helps to choose the safest and most effective ventilator settings for an individual patient at a particular point in the course of a specific disease process that necessitates the use of assisted ventilation. Graphic display of flow allows to judge whether the chosen in- and expiratory times are sufficient for equilibration of forces.

Clinical relevance: Therefore, in practical terms, a stiff RDS lung with low compliance and low resistance will empty very quickly on expiration and has a short time constant and therefore, can be ventilated using high ventilator rates or even by using high-frequency ventilation. However, in BPD lungs, which have high compliance and high resistance, the lung needs a longer time to fill and empty and has a long time constant, and therefore lower rates are more useful for ventilatory support.

3. Basic mechanisms of gas transport in neonatal mechanical ventilation

The main mechanisms of gas transport are the pressure gradient and the concentration gradient. In airways, the mechanism of gas transport during inspiration is convection or bulk flow along with a difference in pressure at the origin (outside positive atmospheric pressure) and destination of the gases (negative intrapleural pressure). For alveoli and pulmonary capillaries, the mechanism of gas exchange (O_2 uptake and CO_2 elimination) is molecular diffusion by Brownian motion through the difference in the concentration between gases in contagious spaces. Fick's equation governs the movement of any gas across a semipermeable membrane for diffusion ($dQ/dt = k \times A \times dC/dl$). Where dQ/dt is the rate of diffusion in ml/min, k is the diffusion coefficient of the gas, A is the area available for diffusion, dC is the concentration difference of molecule across the membrane, and dl is the length of the diffusion pathway. It is important to note that the negative intrathoracic pressure during spontaneous or negative pressure ventilation facilitates the venous return to the heart. Positive pressure ventilation alters this physiology and inevitably leads to some degree of the impedance of venous return, adversely affecting cardiac output. However, positive pressure ventilation causes a left ventricular afterload reduction, which may be beneficial in left ventricular heart failure.

3.1. Tidal volume and minute ventilation

The amount of gas inspired in a single spontaneous breath or delivered through an endotracheal tube during single mechanical inflation is called tidal volume (V_T). In neonates, the average tidal volume is thought to be 4–6 ml/kg. Minute ventilation (V_E) is calculated from tidal volume (V_T) in milliliters multiplied by the number of inflations per minute or respiratory frequency (f). It is approximately 0.2–0.3 L/min/kg in healthy neonates.

Clinical relevance: If using a volume targeted mode, the tidal volume to be aimed for should be approximately 4–6 mL/kg, and alarm limits for minute ventilation may be set at 10–20% above and below the limit of 0.2–0.3 L/min/kg [7–10].

3.2. Anatomic dead space

The portion of the incoming VT that fails to arrive at the level of the respiratory bronchioles and alveoli but instead remains in the conducting airways occupies the space known as the anatomic dead space. Dead space is dependent on gestational age and weight and approximates 1.5 ml/kg. As instrumental dead space (tube connector, flow sensor, Y-piece) is usually fixed, total dead space (anatomic + instrumental dead space) measured per kg body weight is usually larger in extremely low birth weight infants than in more mature infants [11].

3.3. Alveolar dead space

A portion of VT may be delivered to un-perfused or under-perfused alveoli. Because gas exchange does not take place in these units, the volume that they constitute is called alveolar dead space.

3.4. Physiologic dead space and wasted ventilation

Together, anatomic dead space and alveolar dead space make up total or physiologic dead space (V_{DS}). The ratio of dead space to V_T (V_{DS}/V_T) defines wasted ventilation, the proportion of tidal gas delivered that is not involved in actual gas exchange. Overall, rapid shallow breathing is inefficient because of a high V_{DS} to V_T ratio.

Clinical relevance: As a 23-week, 500 g preterm infant would have a larger dead space, one would usually start at 5 ml/kg Tidal Volume when compared to a term baby, where one would probably aim for 4 ml/kg at the start of volume ventilation.

4. Oxygenation

Factors mainly increase the oxygen uptake through lungs in invasive neonatal conventional ventilation. A) increasing PAO_2 via increasing fraction of inspired O_2 (FiO_2) and B) optimizing lung volume (optimizing ventilation (V)-to-perfusion (Q) matching and

increasing the surface area for gas exchange by increasing mean airway pressure, and C) maximizing pulmonary blood flow (preventing blood from flowing right to left through extra pulmonary shunts).

Clinical relevance: Five different ways to increase mean airway pressure in conventional mechanical ventilation noted in the literature are shown in Fig. 5. Any maneuver to increase the area under the curve (a) improves oxygenation in neonates with alveolar lung disease such as RDS. The maneuvers include 1) increase in inspiratory flow rate, producing a more square-wave inspiratory pattern; 2) increase peak inspiratory pressure; 3) increasing the i-time; 4) increasing PEEP, and 5) increase the ventilatory rate by reducing expiratory time without changing the inspiratory time. Both interventions two and or five may result in inadvertent hyperventilation, which is also undesirable. Reversing the inspiratory-to-expiratory ratio or prolong inspiratory time (i-time, 3) without changing the rate – is a potentially dangerous measure and is rarely used today. Increasing positive end-expiratory pressure (PEEP) is probably the safest, most effective and most commonly used way to achieve a higher mean airway pressure, to open lung volume and thus to improve oxygenation in alveolar lung disease.

5. Ventilation

Ventilation is the process of removal of carbon dioxide from the lungs. The retention of CO_2 causes respiratory acidosis and deterioration of the pH. However, it is also recognized that aggressive clearance of CO_2 to very low levels is equally harmful as it may decrease cerebral blood flow and cause brain ischemia in preterm infants, primarily if it occurs acutely.

Clinical relevance: Carbon dioxide removal in invasive neonatal conventional ventilation can be achieved by increasing tidal volume (V_t) or increasing the ventilator rate (which is controlled either directly or by altering the inspiratory and/or expiratory time). Ventilators may have different types of controls on tidal volume. In volume-controlled ventilation, tidal volume delivered into the ventilator circuit is manipulated directly. This mode of ventilation is mostly affected by a leak around the endotracheal tube. In pressure limited ventilation, tidal volume is controlled by the difference between peak inspiratory pressure and positive end-expiratory pressure (delta P). Adjustments in tidal volume may be made by measuring the expired tidal volume and changing the delta P based on that measurement.

6. Perfusion

Optimization of lung volume decreases pulmonary vascular resistance and increases pulmonary blood flow. The two types of pulmonary blood vessels seen in the lungs are A) alveolar vessels mainly composed of capillaries with its diameter mainly influenced by the intra-alveolar pressure and the hydrostatic pressure in capillaries and B) extra-alveolar vessels mainly composed of arteries and veins in interstitial tissue with its diameter mainly influenced by lung volume. Both atelectasis and over-expansion can affect lung compliance by changing the lung volume, which in turn results in increased pulmonary vascular resistance. In hypoxic individuals, an increase in oxygen tension in alveoli (PAO_2) and in arterial blood (PaO_2) can increase the pulmonary perfusion. Hypoxemia increases pulmonary vascular resistance. During spontaneous breathing, ventilation (V) and Perfusion (P) ratio are higher in lower (dependent) lobes compared to upper (non-dependent) lobes of the lung. Ideally, the ratio is 1. If lung areas are under-ventilated but normally perfused or normally ventilated but over perfused, then the ratio will be less than 1. In lung areas, which are over-ventilated and normally perfused or usually ventilated and under perfused, then the ratio will be more than 1.

Clinical relevance: A chest X-ray allows to detect hyper-expanded lungs or lung areas. Unexplained increases in PCO_2 in an improving RDS following surfactant could be due to hyper-expansion, resulting in decreased ventilation and thus CO_2-removal, and decreased blood pressure due to decreased venous return to the heart.

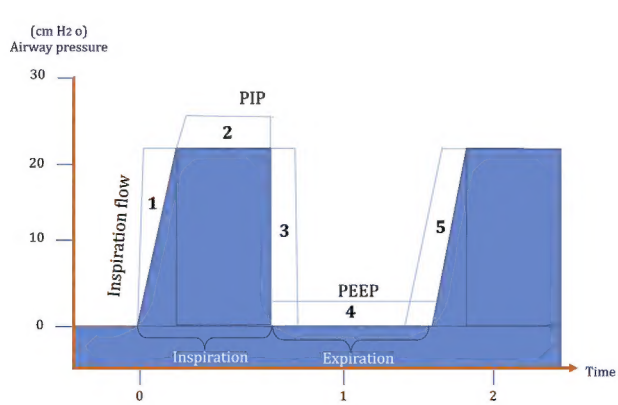

Fig. 5. Five different ways to increase mean airway pressure (Adopted from Goldsmith et al.).

7. Conclusion

In summary, a good understanding of basic physiology and, in particular, concepts in neonatal lung physiology is essential for successful respiratory support. This allows a physiology-based approach and application of these concepts in daily practice for decision making regarding the use of modes and settings of mechanical ventilation, with the ultimate aim of providing adequate gas exchange and minimising lung injury. It is clear that the strategies we use will ultimately affect both short- and long-term pulmonary outcome.

Ethical statement

The authors declare that they have no known ethical issues identified in construction of this manuscript.

Declaration of competing interest

No conflicts between authors.

CRediT authorship contribution statement

Aravanan Anbu Chakkarapani: Conceptualization, Writing - original draft. **Roshan Adappa:** Writing - review & editing. **Sanoj Karayil Mohammad Ali:** Writing - review & editing. **Samir Gupta:** Writing - review & editing. **Naharmal B. Soni:** Writing - review & editing. **Louis Chicoine:** Writing - review & editing. **Helmut D. Hummler:** Supervision, Writing - review & editing.

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